REMARKS

Claims 1, 10-11 and 13-18 are presently pending in the captioned application. Subsequent to the enclosed amendment, claims 1 and 13-14 are currently amended, claims 2-9 and 12 are cancelled and claims 10 and 15-18 are pending as previously presented. Claim 11 is pending as originally filed.

Claim 1 has been amended to recite a "process" for the production of a polymeric micelle. Support for the amendment can be found in the claim itself. Dependent claims 13 and 14 have been amended accordingly to recite a "process" rather than a "production process". No new matter within the meaning of § 132 has been added.

A declaration is submitted under 37 C.F.R. § 1.132 containing evidence that the process taught by the cited reference JP 11-335267 ("Ichiro *et al.*") cannot result in the presently claimed invention. Applicants have met their burden to demonstrate that Ichiro *et al.* is inoperative because the process of producing medicine-encapsulated polymer micelle made according to the block copolymer and other production components of the reference cannot result in the formation of a polymeric micelle.

Accordingly, Applicants respectfully request the Examiner to enter the indicated amendments of Appendix A and allow all the presently pending claims in view of the submitted evidence and following remarks.

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1. **Rejection of Claims 1, 10-11, 13-18 under 35 U.S.C. § 102(b)**

The Office Action rejected claims 1, 10-11 and 13-18 under 35 U.S.C. § 102(b) as being unpatentable by JP 11-335267 ("Ichiro *et al.*"). The Office Action stated:

> Ichiro teaches the same block copolymer compositions as the applicant and the method for producing them, the composition forms micelles and are used to deliver water scarcely soluble drugs (including camptothecin), all of the above are within the limits specified by the applicants claims. See abstr, claims 1-7, [0014]-[0018]. With regard to claims 1, 13-14, which are product by process claims, the product disclosed by the prior art is identical to the claimed product, even though (it is made by a somewhat different process/the prior art is silent on the method of making). There is no evidence to show that the claimed process imparts any patentable distinction between the claimed products and that of the prior art. Regarding the phrases "micelle in water can stably be maintained in a drug concentration of at least 3, 6, 10 mg/ml", in claims 10, 15-18 was given no patentable weigh since Ichiro teaches a very broad range of concentrations for the drug in the composition, the burden is now shifted to the applicants to shows that those concentration do not encompass the claimed concentration of the drug in the micelle solution. It is also inherent since the polymers and drugs are the same the inventor would optimized the solution so that it can be stable at various drug concentrations, thus the examiner gave no patentable weight to the drug concentrations in solution for claims 10, 15-18.

Ichiro *et al.* does not anticipate the presently claimed "process" for the production of a polymeric micelle charged with a water-scarcely soluble drug of claims 1 and 13-14 because the reference fails to teach the presently claimed "oil-in-water (O/W) type emulsion".

Ichiro *et al.* also does not anticipate the presently claimed "composition" of claims 10 and 15-

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18 because the reference is inoperative as shown by the submitted § 1.132 declaration. The presently claimed drug-encapsulated polymeric micelle cannot be manufactured from a water-scarcely soluble drug and PEG-P (Asp, BLA) in accordance with the method taught by Ichiro *et al.*

Moreover, Ichiro *et al.* teaches a different block polymer from that of the claimed invention and even goes so far as to teach away from the claimed block copolymer. For example, Table 1, in Example 2 of Ichiro *et al.* shows that only PEG-P (C_{16}, BLA) results in a homogenous solution (successful encapsulation of medicine with polymeric micelles). However, the block copolymer, PEG-P (C_{16}, BLA) of Ichiro *et al.* is not the same as the presently claimed block copolymer of formulas (I) and (II) because the R moiety of the PEG-P (C_{16}, BLA) of Ichiro *et al.* is not hydrogen (H). In other words, Ichiro *et al.* specifically teaches away from the use of hydrogen (H) for the moiety CH_2COOH in the presently claimed block copolymer of Formulas (I) and (II).

Rule of law

The Federal Circuit held that anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Those elements must either be inherent or expressly disclosed and must be arranged as in the claim. In re Bond, 15 USPQ2d 1566 (Fed. Cir. 1990). Additionally, there must be no difference between the claimed invention and the reference disclosed, as viewed by a person of ordinary skill in the art. Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The prior art reference must also be enabling, thereby placing the allegedly disclosed matter in the possession of the public. In re Brown, 329 F.2d 1006, 1011, 241 USPQ 245, 249 (C.C.P.A. 1964). In order to accomplish this, the reference must be so particular and definite that from it alone, without experiment or the exertion of his own inventive skill, any person versed in the art to which it pertains could construct and use it. Id. at 250.

Pending claim 1

The independent "process" claim 1 recites a process for the production of a polymeric micelle charged therein with a water-scarcely soluble drug, comprising the steps of:

> (A) dissolving a water-scarcely soluble drug and a block copolymer having a hydrophilic segment and a hydrophobic segment in a water non-miscible organic solvent to prepare an organic solution, wherein the block copolymer is represented by the following Formula (I) or (II) . . .
>
> (B) mixing the resulting organic solution with an aqueous medium to form an **oil-in-water (O/W) type emulsion,**
>
> (C) vaporizing and removing the above organic solvent from the resulting emulsion to form a polymeric micelle solution charged therein with the above drug, and
>
> (D) subjecting the resulting polymeric micelle solution, if necessary, to supersonic treatment and ultrafiltraton treatment.

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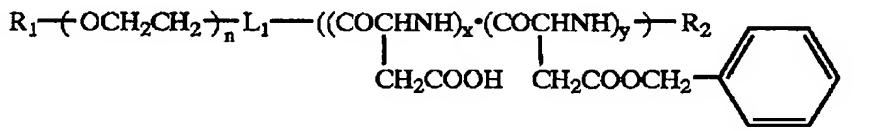
Pending claim 10

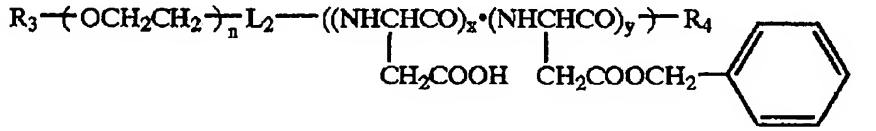
The independent composition claim 10 recites a polymeric micelle originating in a block copolymer charged therein with a drug, wherein the drug is a water-scarcely soluble drug; the block copolymer is represented by the following Formula (I) or (II):

(I)



or

(II)



. . .

Notably, the CH_2COOH moiety is the partially hydrolyzed form of CH_2COOR where R is H.

Analysis

Claims 1 and 13-14 are drawn to a "process" wherein patentable distinctions are imparted by the claimed process steps. Although the Office Action alleged that claims 1 and 13-14 recite a "product-by-process" or composition *per se*; a method of manufacture comprising steps for making the polymeric micelle is clearly recited. This distinction can be seen by the presently claimed limitations providing for (b) mixing, (c) vaporizing and (d) subjecting. As admitted in the Office

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Action, Ichiro *et al.* is silent on the method of making.

Ichiro *et al.* teaches away from the claimed invention by suggesting the use of an "organic water miscible solvent" whereas the present invention claims the use of a "water non-miscible organic solvent". Ichiro *et al.* teaches in the Abstract that the "polymer micelles [*sic*] is obtained by mixing (A) in **the organic water miscible solvent such as dimethylformamide or the like,** (B) the block copolymer ..., and (C) the sparingly water soluble medicine (preferably, camptothecin or the like), **forming polymer micelles including medicine by dialyzing** the mixture into water through the dialysis membrane . . ."

The solvents used in Ichiro *et al.* are clearly not the same as those used in the present invention. For the purpose of forming medicine-encapsulating polymer micelles, Ichiro *et al.* also requires a "dialyzing" treatment which is not suitable for commercial manufacture (or for large-scale manufacture). On the other hand, the presently claimed invention recites an oil-in-water (o/w) type emulsion wherein organic solvent is vaporized and removed from the emulsion, which can be adopted for industrial production. See steps (B) and (C) of claim 1.

Ichiro *et al.* similarly fails to anticipate the composition claims 10 and 15-18. The instant specification discusses Ichiro *et al.* at page 6, lines 18-27 in the background section where it is mentioned that Ichiro *et al.* generically mentions the block copolymers and medicines (or drugs) which are used in the present invention and refers to the formation of polymer micelles which encapsulate said medicines.

However, Ichiro *et al.* provides only one example of the formation of polymer micelles with

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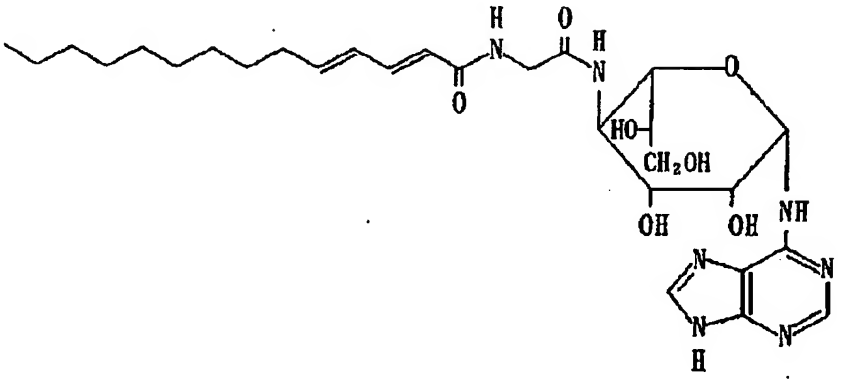
the use of the block copolymers mentioned in which KRN5500 of the following formula is used as a medicine.



This is not sufficient to enable one of ordinary skill in the art to make the same polymeric micelle for the claimed drugs and fails to anticipate the claimed invention.

For example, Table 1 in Example 2 of Ichiro *et al.* shows that the claimed invention cannot be made from the claimed block copolymers. Table 1 of the reference recites:

Table 1

Experiment	Block copoly-mer	(mg)	KRN5500	Solvent	Condition
3	PEG-P (Asp, BLA)	5.0	1.5	DMF	Precipitated
4	PEG-P (Asp, BLA)	5.0	1.5	DMSO	Precipitated
		...			
6	PEG-P (C_{16}, BLA)	5.0	1.5	DMSO	Homogeneous

As is seen in Table 1, when PEG-P (Asp, BLA) was used in Experiments 3 and 4, wherein PEG-P (Asp, BLA) is the only common block copolymer to the reference and the claimed invention, (*i.e.*, in

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the -CH2COOR moiety of block copolymer, R (benzyl group) had partially been hydrolyzed so that R was a hydrogen atom; See [0042] of computer translation of Ichiro *et al.* provided by the JPO), a precipitate was formed in the solution when DMF or DMSO was used as a solvent. Hence, polymeric micelles were not formed when using the block copolymers common to the claimed invention.

Only Experiment 6 of Table 1 of Ichiro *et al.* showed the formation of a "homogeneous solution" (meaning that polymer micelles encapsulating desired medicine were successfully manufactured). However, the block copolymer PEG-P (C_{16}, BLA) used by Experiment 6 is not the same as that of the claimed invention. As mentioned in the instant specification at page 6, lines 18-27, the computer translation of [0025] of Ichiro *et al.* reads as follows

> It uses combining above KRN(s) 5500, and when x is except integer 0, as for R, it is desirable that it is except a hydrogen atom and they are a middle class or a high-class alkyl group.

Consequently, Ichiro *et al.* teaches away from the claimed invention by avoiding the use of a block copolymer wherein R is a hydrogen atom. In other words, Ichiro *et al.* does not teach the use of hydrogen (H) for the moiety **CH_2COOH** in the presently claimed block copolymer of Formulas (I) and (II).

Even when KRN5500, which is the single medicine that is specifically mentioned in Ichiro *et al.* is used, polymer micelles encapsulating the desired medicine are not manufactured when PEG-P (Asp, BLA) is employed. Ichiro *et al.* therefore fails to teach the manufacture of polymer micelles encapsulating medicines (including camptothecin) other than KRN5500, using the presently claimed

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PEG-P (Asp, BLA) as a block copolymer instead of PEG-P (C_{16}, BLA).

With regard to inherency, experimental evidence shows that the prior art cannot produce the presently claimed drug composition of claims 10 and 15-18. See declaration at page 3. Ichiro *et al.* is inoperative because the presently claimed drug-encapsulated polymeric micelle was not successfully manufactured using paclitaxel which is a water-scarcely soluble drug and using PEG-P (Asp, BLA) in accordance with the method taught by Ichiro *et al.*

Accordingly, Applicants respectfully submit that the presently pending claims particularly point out and distinctly claim the subject matter of the invention and request withdrawal of the rejections of the claims under 35 U.S.C. § 102.

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CONCLUSION

In light of the foregoing, Applicants submit that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of the pending claims and allow the pending claims. Favorable action with an early allowance of the claims pending is earnestly solicited.

Respectfully submitted,

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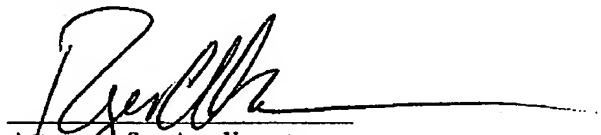

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: 1618
YOKOYAMA; HONZAWA; OGAWA	)	Examiner: J. W. Rogers
Serial No. 10/666,384	)	
Filed: September 22, 2003	)	

For: **PRODUCTION PROCESS FOR POLYMERIC MICELLE CHARGED THEREIN WITH DRUG AND POLYMERIC MICELLE COMPOSITION**

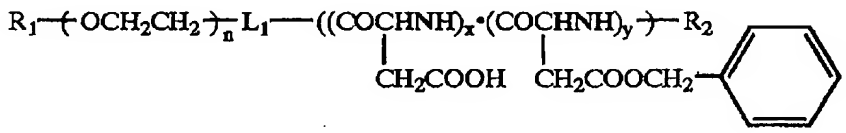
Appendix A

1. (Currently amended) A ~~production~~ process for the production of a polymeric micelle charged therein with a water-scarcely soluble drug, comprising the steps of:

(A) dissolving a water-scarcely soluble drug and a block copolymer having a hydrophilic segment and a hydrophobic segment in a water non-miscible organic solvent to prepare an organic solution,

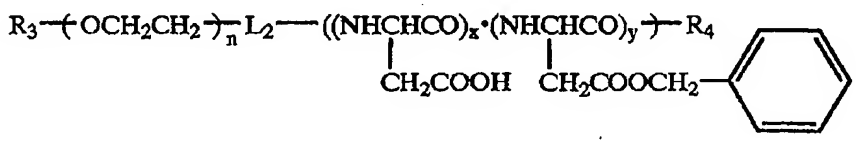
wherein the block copolymer is represented by the following Formula (I) or (II)

(I)



or

(II)



wherein R_1 and R_3 represent a hydrogen atom or a lower alkyl group; R_2 represents a hydrogen atom, a saturated or unsaturated C_1 to C_{29} aliphatic carbonyl group or an arylcarbonyl group; R_4 represents a hydroxyl group, a saturated or unsaturated C_1 to C_{30} aliphatic oxy group or an aryl-lower alkyloxy group; L_1 represents a linkage group selected from the group consisting of -NH-, -O- and -OCO-Z-NH- (wherein Z represents a C_1 to C_4 alkylene group); L_2 represents a linkage group selected from -OCO-Z-CO- and -NHCO-Z-CO- (wherein Z represents a C_1 to C_4 alkylene group); n represents an integer of 10 to 2500; x and y may be the same or different and represent integers the total of which is 10 to 300; x to y falls in a range of 7 : 3 to 1 : 3,

(B) mixing the resulting organic solution with an aqueous medium to form an oil-in-water (O/W) type emulsion,

(C) vaporizing and removing the above organic solvent from the resulting emulsion to form a polymeric micelle solution charged therein with the above drug, and

(D) subjecting the resulting polymeric micelle solution, if necessary, to supersonic treatment and ultrafiltraton treatment.

Claims 2-9 (Cancelled)

10. (Previously presented) A composition comprising a polymeric micelle originating in a block copolymer charged therein with a drug, wherein the drug is a water-scarcely soluble drug; the block copolymer is represented by the following Formula (I) or (II):

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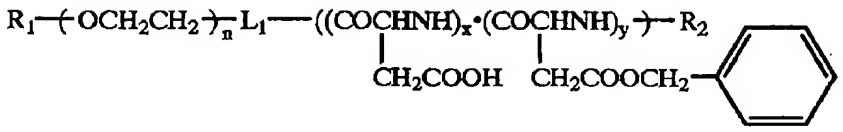
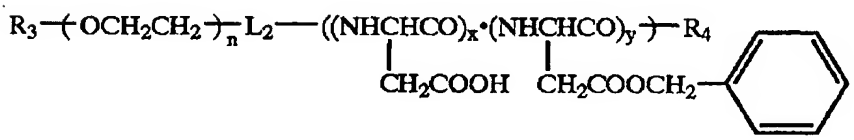
(I)



or

(II)



wherein R_1 and R_3 each represent a hydrogen atom or a lower alkyl group; R_2 represents a hydrogen atom, a saturated or unsaturated C_1 to C_{29} aliphatic carbonyl group or an arylcarbonyl group; R_4 represents a hydroxyl group, a saturated or unsaturated C_1 to C_{30} aliphatic oxy group or an aryl-lower alkyloxy group; L_1 represents a linkage group selected from the group consisting of -NH-, -O- and -OCO-Z-NH- (wherein Z represents a C_1 to C_4 alkylene group); L_2 represents a linkage group selected from -OCO-Z-CO- and -NHCO-Z-CO- (wherein Z represents a C_1 to C_4 alkylene group); n represents an integer of 10 to 2500; x and y may be the same or different and represent integers the total of which is 10 to 300; x to y falls in a range of 7 : 3 to 1 : 3; and x and y each are present at random; a micelle solution prepared by dissolving or dispersing the above micelle in water can stably be maintained in a drug concentration of at least 3 mg per ml of the solution.

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11. (Original) The composition as described in claim 10, wherein the drug is selected from the group consisting of paclitaxel, docetaxel, camptothecin and topotecan.

Claim 12 (Cancelled)

13. (Currently amended) The ~~production~~ process as described in claim 1, wherein the drug and the block copolymer are used in a weight ratio of 1:10 to 3:10.

14. (Currently amended) The ~~production~~ process as described in claim 1 wherein the drug is selected from the group consisting of paclitaxel, docetaxel, camptothecin and toptecan.

15. (Previously presented) The composition as described in claim 10, wherein the drug is selected from the group consisting of paclitaxel, docetaxel, camptothecin and topotecan, and wherein said micelle solution can stably be maintained in a drug concentration of at least 6 mg per ml of the solution.

16. (Previously presented) The composition as described in claim 10, wherein the drug is selected from the group consisting of paclitaxel, docetaxel, camptothecin and topotecan, and wherein said micelle solution can stably be maintained in a drug concentration of at least 10 mg per ml of the solution.

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17. (Previously presented) The composition as described in claim 10, wherein the drug is paclitaxel and an analogue thereof, and wherein said micelle solution can stably be maintained in a drug concentration of at least 6 mg per ml of the solution.

18. (Previously presented) The composition as described in claim 10, wherein the drug is paclitaxel and an analogue thereof, and wherein said micelle solution can stably be maintained in a drug concentration of at least 10 mg per ml of the solution.

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